REMARKS

In the Office Action mailed February 18, 2005:

Claims 11, 48, 49 and 58 were indicated to be allowable.

Claims 1-8, 10, 12, 25-27, 31, 32, 34, 36-37, 50-and 60 were rejected under 35 U.S.C. 103(a) as anticipated by Frazier et al.(WO 01/93930) in view of Pisano et al. (US 5,928,207).

Claims 9, 13-15, 18 and 20-24 were rejected under 35 U.S.C. 103(a) as unpatentable over Frazier et al. in view of Pisano et al., as applied to claims 1-8, 10, 12, 25-27, 31, 32, 34, 36-37, 50, and 60 above, further in view of Say et al.

Claims 16 and 17 were rejected under 35 U.S.C. 103(a) as unpatentable over Frazier et al. in view of Pisano et al. and Say et al, as applied to claims 9,13-15, 18, 19 and 21-24 above, further in view of Meade et al. (US 5,770,369)

Claim 20 was rejected under 35 U.S.C. 103(a) as unpatentable over Frazier et al. in view of Pisano et al. and Say et al., as applied to claims 9,13-15, 18, and 20-24, further in view of Meade et al.

Claims 51-53 were rejected under 35 U.S.C. 103(a) as unpatentable over Frazier et al. in view of Pisano et al and Hodges et al, (6,612,111).

Claim 57 was rejected under 35 U.S.C. 103(a) as unpatentable over Frazier et al. in view of Pisano et al. and Lin et al..

CLAIM AMENDMENTS AND ADDITIONS

Claims 51, 52 and 53 have been cancelled.

Claims 61-65 have been added.

Support for these claims can be found in the specification. Microprobe thicknesses of 50 micrometers and 100 micrometers are disclosed in paragraphs 95 and 13 respectively. The use of a silicon wafer as a substrate is also disclosed in paragraph 95; 500 and 300 micrometer thick wafers are readily available. As such, no new matter has been added with these amendments

CLAIM REJECTIONS

Claims 51-53

The Applicants submit that the rejections of claims 51, 52 and 53 are moot in view of cancellation of these claims.

Claims 1-8, 10, 12, 25-27, 31, 34, 36-37, 50 and 60

Claims 1-8, 10, 12, 25-27, 31, 34, 36-37, 50 and 60 were rejected under 35 U.S.C. 103(a) as anticipated by Frazier et al.(WO 01/93930) in view of Pisano et al. (US 5,928,207).

Frazier et al. describe only one method of microneedle fabrication at (page 13, line 9 page 15, line 5), in which the microneedle base, side walls, and top are formed from material deposited in sequence. Further, Frazier et al. teach that microneedles made out of etched silicon are brittle and tend to break easily, providing relatively poor mechanical durability (page 2, lines 18-22). Frazier et al. thereby do not teach, and in fact teach away from, a microprobe formed from a single piece of etched silicon as are both Pisano's lancet and Applicants' microprobe.

Pisano et al. disclose both a hollow microneedle with bottom and side walls formed by a channel in the single-crystal silicon body and a polysilicon top cap, and a single-crystal silicon lancet microprobe without channel or top cap. Pisano et al. further disclose a hypodermic injection needle with "integrated circuitry for chemical concentration monitoring .... and the control of fluid flow, such as through an integrated valve or pump." (column 1, lines 17-22), and that their undoped hollow microneedle may incorporate such integrated circuitry (column , lines 34-36) in the channel. However, nowhere do Pisano et al. disclose or suggest combining a sensing element or biosensor with the solid lancet microprobe. Thus, by teaching a hollow microneedle with sensing capabilities incorporated inside the channel, but limiting the solid silicon microprobe to use as a lancet without any concept of added elements, the combination of Frazier with Pisano et al. does not teach, and in fact teaches away from, a biosensor integrated into a microprobe device as set forth in claim 1.

Furthermore, claims 2-8, 10, 12, 25-27, 31, 34, 36 and-37 depend from claim 1 and recite additional features therefor, and claim 60 depends from claim 5. As such, and for the same reasons set forth above, the applicants submit that these dependent claims define an invention suitable for patent protection.

Claims 26 and 27

Further with regard to claims 26 and 27, the hollow microneedles of Frazier et al. and Pisano et al. are intended for use in either fluid injection or extraction, depending on the direction of flow through the bore or channel of the microneedle Both references utilize a pumping mechanism to provide fluid flow through the channel of the hollow microneedle in the desired dirction. Both references disclose that a sensor can be incorporated within the channel.

As discussed above, Pisano et al disclose a mechanism for " control of fluid flow, such as through an integrated valve or pump." (column 1, lines 17-22) in the microneelde channel. In Frazier et al., either a micropump within the channel of the microneedle itself (page 7, line 6) , or an external syringe (page, lines) is used to flow the fluid sample through the pointed tip of the needle and/or through the entry port, up the channel over the optical biosensor, and out the exit port. Some pumping mechanism is required for either device to "provide real-time analysis of a fluid being sampled such as in a blood analysis system" (page 7, lines 21-22), i.e. to measure changes in analyte concentration. Without a pumping mechanism, although fluid may initially be drawn into the channel and over the sensor by capillary force, flow will immediately stop and the sensor will not respond to concentration changes in the body of fluid to be measured.

The Frazier and Pisano references' placement of the sensor within the needle channel provides the obvious advantage of protecting the sensor during penetration of the tough stratum corneum. However, hollow microneedle devices for use in analyte monitoring suffer from significant disadvantages in terms of MEMS fabrication complexity and cost. In the *in vivo* embodiment of Applicants' biosensor microprobe as recited in claims 26 and 27, the miniaturized biosensor is located sufficiently near the penetration end of the microprobe to come into direct contact with the fluid to be analyzed when the microprobe penetrates the skin (Fig. 1A, paragraph 92). As a result, the biosensor microprobe can measure changes in analyte concentration without the need for fluid transport. Microprobe construction is simpler and less expensive than that of a hollow microneedle because only a single silicon substrate is used. The exact shape of a solid microprobe can be more readily optimized to permit reliable, painless skin penetration. No waste fluid is exuded via an exit port, thus avoiding any blood disposal problem. These advantages are achieved using fewer elements while retaining the same analyte monitoring functionality. No pumping mechanism, nor side and top walls, are required. This retention of

function with fewer required elements provides a strong indicia of unobviousness (see MPEP 2144.04(II)(A).

Claim 50

Claim 50 was previously amended to recite that one or more biosensors are disposed on both sides of the silicon substrate. The use of both sides of the microprobe provides a greater electrode area for each biosensor, allowing a higher signal level and therefore greater sensitivity than is possible when two biosensors and their electrodes must be placed on the same side of the miniaturized probe, or in the channel of a hollow microneedle. The applicants submit that Frazier et al. disclose multiple biosensors on one side of the silicon substrate, but not both sides (see e.g., FIGs. 1A-7B of Frazier et al.). In Frazier et al., the biosensors are deposited on the inside of the hollow needle bore through which the fluid to be analyzed is pumped. There would be no motivation in Frazier et al. to place biosensors on the outer surface of the needle bottom where they would not contact the analyte fluid unless the needle were submerged more deeply than the position of the biosensor, in which case the output signal of the optical biosensor could not be read. Therefore, Frazier et al. do not suggest or teach, and in fact teach away from placement of biosensors on both sides of the (bottom) substrate as set forth in claim 50. Therefore, claim 50 is believed to define an invention suitable for patent protection.

Claim 57

Claim 57 was rejected under 35 U.S.C. 103(a) as unpatentable over Frazier et al. in view of Pisano et al. and Lin et al.

Claim 57 recites that "substantially the entire area of at least the penetration end including the tip, has a substantially equal thickness in the Z direction that is less than the thickness of the body portion." Both Lin et al. and Pisano et al., by contrast, teach microneedles with sharp, thin points. Further, Lin et al.'s fabrication process produces shafts with very thin areas along the edge, as do most of Pisano et al.'s embodiments. At column 4, lines 29-32, Lin et al. note that, with removal of single-crystal silicon with the tip region 86, "the tip is sharper and smaller than the portion of the shaft including single-crystal silicon." Lin et al.'s microneedles use boron doping to define the area and shape of the microneedle, resulting in a thin 12 micrometer rim of boron-doped silicon near the outer perimeter of the needle. Outside of

the boron-doped silicon, the edges of the needle shaft and tip becomes even thinner, consisting of an approximately 3.5 micrometer thick edge of, primarily, silicon nitride.

Figs. 2A and 2B of Lin et al. show a plan view and cross-sectional dimensions, respectively, of Lin's microneedle 10 surrounded by the wafer 46 from which it has been detached. The term "microneedle 10" includes the shank end 12 containing an interface region 11 (the body), the shaft 14 and the tip region 86. As can be seen in Fig. 2B, the entire microneedle is thinned during fabrication, resulting in a 50 micrometer thickness along the shaft (column 4, lines 22-24) and over the shank end (or body) (column 7, lines 39-42). The tip is etched further, removing single-crystal silicon 50 micrometers from the tip end (column 7, lines 42-47) to form a sharp, thin, fragile point.

Pisano et al. comment that sharper tips minimize pain and tissue damage" (column 1 lines 15-17), and disclose that their microneedle is "sharper than prior art microneedles because the processing to form the tip allows for a tip which originates from a nearly infinitesimal point" (column 3 , lines 66-67, column 4, line 1). The Applicant submits that based on the teachings of Lin and Pisano, the discomfort experienced by a subject from microneedle/probe skin penetration would normally be expected to decrease with decreasing probe cross-section and length. However, a clinical trial testing Applicants' silicon microprobe for pain perception produced surprising results. The majority of subjects found the insertion and retraction of 100 micrometer thick microprobes to be painless (see page 4, lines 26-31 of the specification of the present application as filed). Below a thickness of about 50 micrometers, pain sensation was so minimal that thinner probes offered no advantage (page 11, lines 7-11). There is therefore no reason to incur the greater fragility inherent in a sharper needle or a thinner shaft edge. The Applicant submits that this is a surprising result, which is a strong indicia of non-obviousness. Consequently, the constant thickness recited in claim 57 is more that a merely a change in shape and therefore defines over the art of record.

Furthermore, the Applicants submit that the microprobe device of claim 57 omits a key feature of the Pisano et al. and Lin et al. references (namely the tapering or thinning of the shaft in the Z direction in the region of the tip to produce a sharper point) while maintaining its function (minimizing pain and tissue damage). As discussed above, this too is a strong indicia of unobviousness.

The applicants further submit that the rejections of:

claims 9, 13-15, 18 and 20-24 over Frazier et al. in view Pisano et al., as applied to claims 1-8,10,12,25-27,31,32,34,36-37, 50 and 60 further in view of Say et al.,

claims 9 and 13-15 under 35 U.S.C. 103(a) over Frazier et al. in view of Say et al.,

claims 16 and 17 Frazier et al. in view of Pisano et al. and Say et al further in view of Meade et al., and

the rejection of claim 20 over Frazier et al. in view of Pisano et al. and Say et al, as applied to claims 9, 13-15, 18, 19 and 21-24, in further view of Lin et al.,

are overcome by virtue of their dependence on claims that are believed to be allowable for the reasons discussed above.

CONCLUSION

In view of the foregoing, applicants believe that all of the claims are now in condition for allowance. The applicants therefore respectfully request reconsideration of the application and a notice of allowance. If for any reason the Examiner believes any of the claims are not in condition for allowance, he is encouraged to phone the undersigned at (510) 896-8328 so that any remaining issues may be resolved.

Respectfully submitted,

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